CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CHLORPROPHAM

Chemical Code # 000141, Tolerance # 00181
SB 950 # 175

July 28, 1986
September 1994

I. DATA GAP STATUS

Chronic/onco, rat	## Data gap, inadequate study, adverse effect indicated.
Chronic rat:	Data gap, inadequate study, no adverse effect indicated.
Chronic dog:	Data gap, inadequate study, no adverse effect indicated.
Onco rat:	Data gap, no study on file.
Onco mouse:	## Data gap, inadequate study, adverse effect indicated.
Repro rat:	Data gap, inadequate study, no adverse effect indicated.
Terato rat:	## Data gap, inadequate study, no adverse effect indicated.
Terato rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, possible adverse effect.
Chromosome:	No data gap, no adverse effect.
DNA damage:	No data gap, possible adverse effect.
Neurotox:	Not required.

----------**Note, Toxicology one-liners are attached**

All record numbers through record 116175 (volume 32) were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study/worksheet on file but not given a final review. A preliminary one-liner (##) and data gap status is temporarily entered in this Toxicology Summary and are subject to change pending the final review.
File name: T940900
Original: C. Aldous, 7/28/86
Updated: Kishiyama, 9/28/94

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC AND ONCOGENICITY STUDIES:

RAT

035 132116, "24 Month Combined Oncogenicity/Toxicity Evaluation of Chlorpropham in Rats", (J.A. Botta, Jr., T.P.S., Inc. Lab. Project ID 393L-103-055-89, 4/22/93). Chlorpropham, purity 96.2% % 2.0%, admixed with the feed at concentrations of 0 (corn oil), 30, 100, 500 and 1000 mg/kg/day and fed to 10 and 50 Sprague-Dawley rats/sex/group for at least 52 and 102/104 weeks, respectively. Tests were shortened to 102 weeks for females, due to overall low survival. **Possible adverse effect: Testicular interstitial cell tumor for high dose males.** Hemosiderosis of the spleen was observed for males and females; NOEL = 30 mg/kg/day. Tests revealed treatment-related effects to the kidney (mineralized deposits, cysts, pigment, chronic nephritis), liver (hematopoiesis, pigment), Lungs (alveolar macrophages and focal lymphoid infiltrate) and spleen (congestion); and also, increased spleen weight, destruction of red blood cells, cholesterol and bilirubin in the urine for dose groups 500 mg/kg/day and above. UNACCEPTABLE. Upgradeable (confirm dosing material stability). (Kishiyama, 9/26/94).

919925 (previously given as 919925-1). Chronic, Rat, Medical College of Virginia, 6/24/60; Chlorpropham, 50% formulation. Dose levels: 0, 0.02, 0.2, and 2 % in diet. Apparent NOEL = 0.2% (2000 ppm) (weight loss, increased liver and spleen organ to body weight ratios at 20000 ppm). NOT ACCEPTABLE. Not upgradable (too few animals at start, many losses to respiratory disease, too few tissues examined, no individual data, etc.). [Reviewed by Jeff Wong. No disk copy of review].

DOG

38804 (previously given as 919925 or 919925-2). Chronic, Dog, Medical College of Virginia, 6/24/80. Chlorpropham (50% formulation) at concentrations of 0, 0.02, 0.2, and 2 % in diet. Apparent NOEL = 0.2% (2000 ppm) (weight loss, increased liver and spleen organ to body weight ratios at 20000 ppm). NOT ACCEPTABLE. Not upgradable (too few animals at start [2 dogs/sex/group]; too few tissues examined; no individual data, etc.). [Reviewed by Jeff Wong. No disk copy of review].

This dog study is from the same report as the rat chronic study above (see Rec. #919925), and shares common deficiencies. The dog study is inadequate and a replacement study is needed, however toxicity is apparently very low and no significant adverse effects were seen.

032 116175, "One Year Chronic Study of Chlorpropham in Dogs", (J.H. Wedig, T.P.S., Inc., Lab Project ID 393J-502-640-89, 1/20.92). Chlorpropham, purity 96.2%, was admixed with the feed at concentrations of 0 (mazola corn oil), 5, 50, 350 or 500 mg/kg and fed daily to 4 Beagle dogs/sex/group for one year. Food consumption, body weight gains, hematological values (RBC, Hgb, HCT, & MCHC), triiodothyronine (T3), thyroxine(T4) were reduced; total cholesterol, platelets and liver weight increased for 350 and 500 mg/kg/day groups; and thyroid weight increased for 50 mg/kg to 500 mg/kg groups; NOEL = 5 mg/kg. UNACCEPTABLE. Upgradeable (deficiencies: rationale for dose selection and test article stability information). (Kishiyama, 5/16/94).

ONCOGENICITY

Mouse:

035 132117, "18 Month Oncogenicity Evaluation of Chlorpropham in the Mouse", (J.A. Botta, Jr., T.P.S., Inc. Lab. Project ID 393K-002-050-89, 10/21/92). Chlorpropham, purity 96.2% % 2.0%, admixed with the feed at concentrations of 0 (corn oil), 100, 500 and 1000 mg/kg/day and fed to 10 and 50 CD-1* mice/sex/group for at least 52 and 78 weeks, respectively. **Mortality (males)**; amyloidosis of the testes (male); liver and spleen weights (male); reticulocytes (male), mean corpuscular hemoglobin (male) and mean corpuscular hemoglobin concentration counts (male and female); and hematopoiesis in the liver (male and female) increase for the 1000 mg/kg/day groups. Increased incidence of dark eyes and/or bluish tint to the skin of extremities; erythropoiesis in the bone marrow and hemosiderosis in the spleen were observed for 500 and 1000 mg/kg/day male and female groups; NOEL = 100 mg/kg/day. UNACCEPTABLE. Upgradeable (confirm dosing material stability up to two weeks). (Kishiyama, 9/29/94).

TERATOGENICITY

RAT

36950. Teratogenicity, rat, Wil Research Labs, 12/4/81; CIPC Technical (Chlorpropham); 0, 100, 350 and 1000 mg/kg/day by gavage. Maternal toxicity NOEL = 100 mg/kg/day (enlarged spleens at 350 and 1000 mg/kg/day; also slight increase in red stains around eyes, nose, mouth, etc. all dose-related at 350 and 1000 mg/kg/day). Developmental toxicity NOEL = 1000 mg/kg/day (HDT). NOT ACCEPTABLE but upgradable on receipt of dosing solution analysis. [Review by C. N. Aldous, handwritten: No file on disk.

737. Summary of study (#36950) reviewed and considered an upgradeable rat teratogenicity study before by J. Wong. No adverse effects were noted. An UNACCEPTABLE study due to insufficient information.

RABBIT

** 36951. Teratogenicity, rabbit, Huntingdon Research Center, March 8, 1983. Chlorpropham (= CIPC), Technical. Doses of 0, 125, 250, and 500 mg/kg/day by gavage. NOEL, maternal = 250 mg/kg/day (lower weight gain, abortions, some clinical signs). NOEL, developmental toxicity = 250 mg/kg/day (increase in embryonic plus fetal deaths). ACCEPTABLE. Review by C. Aldous.

An ACCEPTABLE rabbit teratogenicity study (Rec. #036951) was originally reviewed by Dr. Jeff Wong. He judged the study to represent significant adverse effects on the basis of scolioses in three fetuses (2 litters): malformations located in the cervical, thoracic, and thoraco-lumbar areas, respectively. The dose associated with these malformations was rather high (500 mg/kg/day), and was sufficient to cause various clinical signs in the dams. Two abortions at that dose level were probably attributable to treatment. In a preliminary study, doses of 800 mg/kg/day were sufficiently toxic to dams that the investigation was terminated after 7 days for humane reasons. The primary study was re-examined by Drs. C. N. Aldous and J. A. Parker, and these reviewers determined that indication of a "possible adverse effect" was not warranted under these circumstances. The following is a quote from these latter two reviewers, which was handwritten on the review worksheet: "This study was previously reviewed by Jeff Wong, (5/30/85, Vol. 007, Rec.# 736). In light of the "EPA

Hazard Evaluation Division Standard Evaluation Procedure, Teratology Studies", June 1985, the results seen in this study would not be considered a possible significant effect as they only occurred at a level that also produced maternal toxicity." (Signed: J. A. Parker and Charles N. Aldous on 1/27/86).

REPRODUCTIVE EFFECTS

RAT

036944, 036945, and 036946. Reproduction, Rat, Bio/Dynamics; July 5, 1983. CIPC = Chlorpropham, tech., at doses of 0, 1000, 3000, and 10000 ppm in diet. No significant adverse effects were noted. Parental toxicity NOEL = 1000 ppm (decreased adult growth, both sexes; also brown pigments increased in amounts in reticuloendothelial cells). Reproductive NOEL = 1000 ppm (decreases in pup weights during lactation). UNACCEPTABLE. Upgradable (can be made acceptable on receipt of individual parental animal in-life observation data). [Handwritten worksheet: no file on disk]. (Reviewed by C. N. Aldous).

735. Earlier summary report of 036944, 036945, and 036946 examined by Jeff Wong.

MUTAGENICITY: Toxicology Summary on Mutagenicity Studies. (Joyce F. Gee, 4/29/86).

MUTAGENICITY, GENERAL

022, 023, 36948, 49. Two volume report of an international study to evaluate the mutagenicity of a series of compounds in different tests and laboratories using a common source of the 42 chemicals. Volume 22 contains the background summaries, volume 23, the individual reports. Chlorpropham (chloropropham, isopropyl-_m-chlorocarbanilate or isopropyl-N-(3-chorophenyl)carbamate) was included as a structural control for urethane. Urethane was considered the carcinogen and chlorpropham as the non-carcinogen based on studies in mice, rats, hamsters, IARC Monographs, 1976.

MUTAGENICITY, GNMU

Bacteria:

** 023 42331 (Institute of Animal Genetics, Scotland, 1979.) JGR, 2/21/86. *Salmonella.* Acceptable with no increase in reversion rate. *E. coli* also included. Mutagenicity was tested with and without activation up to 10,000 ug/plate. Chlorpropham, 98%. This is Chapter 25; included are 16 other chapters on *Salmonella* studies and *E. coli*, many with no data but a "+" or "-" for the result. See Evaluation Sheet for comments on these other studies.

Mammalian Cells:

** **023 42335** (SRI, 1979) JGR, 2/21/86. Mouse lymphoma. **ACCEPTABLE with positive adverse effects for increased forward mutation frequency**. Chlorpropham, 98%, at 0-225 ug/ml minus activation; 0-31.5 ug/ml with rat liver S9 activation. Duplicate cultures. **Response was increased over 2-fold with activation compared with the negative control**. [see 36947 below].

021 36947 (Microbiological Assoc., 1983) JGR, 1/21/86. Not part of the international study. Mouse lymphoma. UNACCEPTABLE **with a (?) positive effect.** Chlorpropham, lot 237-2778, no purity, tested at 0-75 ug/ml with no activation and 0-100 ug/ml with rat liver activation, 4 hour

incubation, 48 hour expression time. Marginal effect - S9 but no repeat trial. Because of positive response in 42355 above, it is important that the study be confirmed. It is recognized that the mouse lymphoma gives more false positives than CHO, for instance, but on the evidence presented in the two reports on hand, no conclusion can be reached except potential genotoxicity.

023 42358 (Sandoz, 1979). JGR, 2/24/86. Mouse micronucleus. Chlorpropham, 98%, 2/sex/group, 0, 35, 70 or 140 mg/kg, dosed i.p. twice and sacrificed at 6 hours, No adverse effect. Incomplete, unacceptable. This protocol is at variance with that in the guidelines, an inadequate number of animals per group and no evidence the MTD was reached.

** 023 42352 (SRI, 1979), JGR, 2/24/86. Sister chromatid exchange. Acceptable with no adverse effect reported. Chlorpropham, 98%, tested in CHO for SCE's and in rat liver epithelial cells for aberrations. 0-300 ug/ml for CHO, up to 60 ug/ml (50% viability) for rat liver cells.

MUTAGENICITY, DNA/OTHER

** 023 42322 (Glaxo, 1979). JGR, 2/21/86. *E coli* DNA repair. Acceptable no adverse effect reported. Chlorpropham, 98%, in a series of assays with erratic results, some "+" and some "-". No activity in the presence of S9. See Evaluation Worksheet for discussion of several studies.

** 023 42344 (Leningrad, 1979). JGR, 2/12/86. *Sacharomyces* mitotic recombination. Acceptable with no adverse effect. Tested up to 333.33 ug/plate with and without activation.

** **023 42346** (Univ. College of Swansea, Wales, 1979). JGR 2/21/86. Acceptable **with positive adverse effect in mitotic gene conversion in *Sacchromyces*** strains. Chlorpropham, 95%, up to 750 ug/ml with and without activation. **The positive effect was seen in the presence of cytotoxicity.** The reports tend to consider the results as false positives based on notion than the test article is a non-carcinogen.

** 023 42351 (Univ. of York, Eng., 1979) JGR, 2/21/86. UDS. Acceptable with no adverse effect; Chlorpropham, 98%, in HeLa cells and skin fibroblasts, with and without activation up to 100 ug/ml. No induction of UDS in HeLa and a marginal effect in skin fibroblasts. Consensus of reviewers was a "-".

023 42356 (Huntingdon Res., 1979). JGR, 2/12/86. Cell transformation. Unacceptable **with a positive adverse effect in BKH cells**. Chlorpropham, 98%. Tested from 0 to the LC50. Incomplete with missing information for evaluation. Despite both reports (see also 42357) being inadequate, the positive response cannot be ignored.

In summary, possible positive genotoxic effects have been identified in mouse lymphoma mutation assay, yeast mitotic gene conversion and cell transformation. Although chlorpropham was included as a non-carcinogen, this does not exclude genotoxic effects leading to other detrimental biological endpoints. The opinion offered by the authors of the international study is that the positive effects were seen in some less frequently used tests and the meaning is less well understood. Also, some investigators think the mouse lymphoma is more "sensitive" than CHO or V79 for mutation. The positive effect with *Saccharomyces* gene conversion was in the presence of cytotoxicity and considered as "false positive" based on the presumption that chlorpropham is an non-carcinogen, keeping in mind that this identification may be based on marginal studies. The two reports are summarized under 42356 showing increase in cell transformation are unacceptable due to missing information and the significance is difficult to evaluate but since two independent reports this finding, it cannot be readily dismissed. Studies in other categories (see above) do not indicate adverse effects as conducted. Given a complete

battery of adequate 950-type studies and the inconsistent pattern of genotoxic effects, the positive findings must be viewed as uninterpretable without further understanding of mechanisms.